

Methotrexate osteopathy in rheumatic disease

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Abstract

Objective—To determine whether two adults with stress fractures receiving low weekly doses of methotrexate had methotrexate osteopathy.

Case reports—Two adult patients developed features consistent with methotrexate osteopathy while receiving low weekly doses of methotrexate.

Methods—Iliac crest biopsy samples were taken and bone histomorphometry carried out.

Results—Symptoms resolved when the methotrexate was discontinued. Bone histology showed changes consistent with osteoblast inhibition by methotrexate.

Conclusions—When given in low doses for prolonged periods, methotrexate may have adverse effects on bone, particularly in post-menopausal women.

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Methotrexate, a competitive inhibitor of folic acid metabolism, is widely used in the treatment of rheumatic disease, particularly psoriatic and rheumatoid arthritis.¹ The major side effects on the liver and gastrointestinal tract are well recognised.² Methotrexate osteopathy has been reported in children in association with high doses used for the treatment of malignancies in childhood.³⁻⁷ It is characterised by a triad of bone pain, osteoporosis, and fractures.⁷ We report the cases of two adults who developed methotrexate osteopathy who, to our knowledge, are the first to be described with the disorder during long term treatment with low doses of methotrexate used in the treatment of rheumatic disease.

Case reports

CASE 1

A 58 year old white woman presented with bilateral ankle pain of several months' duration associated with swelling of the right leg and ankle. There was no history of trauma. She had been taking methotrexate for skin psoriasis for five years and, after the death of her dermatologist, began to treat herself with doses as high as 25 mg methotrexate weekly. She smoked 20 cigarettes each day, did not drink alcohol, was post-menopausal, and had never taken corticosteroids.

On examination there was extreme tenderness to palpation along both distal tibiae. The range of movement of her ankle and knee joints was normal, and there was no evidence of synovitis. She had thin hair, mucositis of the

mouth, but no psoriatic skin rash. Initial radiographs of her ankles showed a poorly defined area of sclerosis at the distal left tibial metaphysis (figs 1A and B). A bone scan showed increased blood pool activity and delayed technetium uptake in the metaphyseal regions of the proximal and distal tibiae, suggestive of stress fractures (fig 1C).

Radiographs performed six months later showed bilateral distal tibial fractures and a proximal left tibial fracture, but no abnormalities in the hands, feet, or sacroiliac joints.

A complete blood count was normal. Serum B-12, folate and red cell folate, and serum biochemistry were normal. Serum alkaline phosphatase was 100 U/l (normal range 20-95 U/l), but other liver function tests were normal. Serum calcium (2.35 mmol/l), phosphate (1.05 mmol/l), and thyroid function tests were normal. Serum parathyroid hormone was 0.26 ng/ml (normal <0.4 ng/ml), 25 hydroxyvitamin D 38 nmol/l (18-128 nmol/l), and 1,25-dihydroxyvitamin D 70 pmol/l (46-207 pmol/l). The bone mineral density of the lumbar spine was reduced (table) and iliac crest bone histomorphometry (table) showed reduced osteoid surfaces and osteoid thickness and low bone formation rates (fig 2). There was no evidence of osteomalacia or hyperparathyroidism.

Methotrexate was stopped with a gradual resolution of bone pain, but the tenderness over the distal tibiae and the proximal left tibia persisted for several months. Twelve months later the patient reported weightbearing pain in the right forefoot. A technetium bone scan showed features compatible with a metatarsal fracture of the right foot. In addition there appeared to be a reduction in isotope uptake in the proximal and distal tibiae compared with previous scans.

CASE 2

A 75 year old white woman with a 15 year history of seropositive, erosive, nodular rheumatoid arthritis had been treated with methotrexate, 10 mg/week, for six years. She presented with a history of several months of left leg and ankle pain, which on examination showed marked swelling and tenderness predominantly over the distal left tibia. Examination showed evidence of a clinically inactive chronic deforming arthritis. She had never received corticosteroids by mouth. Her past history included a total thyroidectomy which required thyroxine replacement of 50 µg/day to maintain a euthyroid biochemical status. She had smoked 10-15 cigarettes a day in the past, but did not drink alcohol. She was

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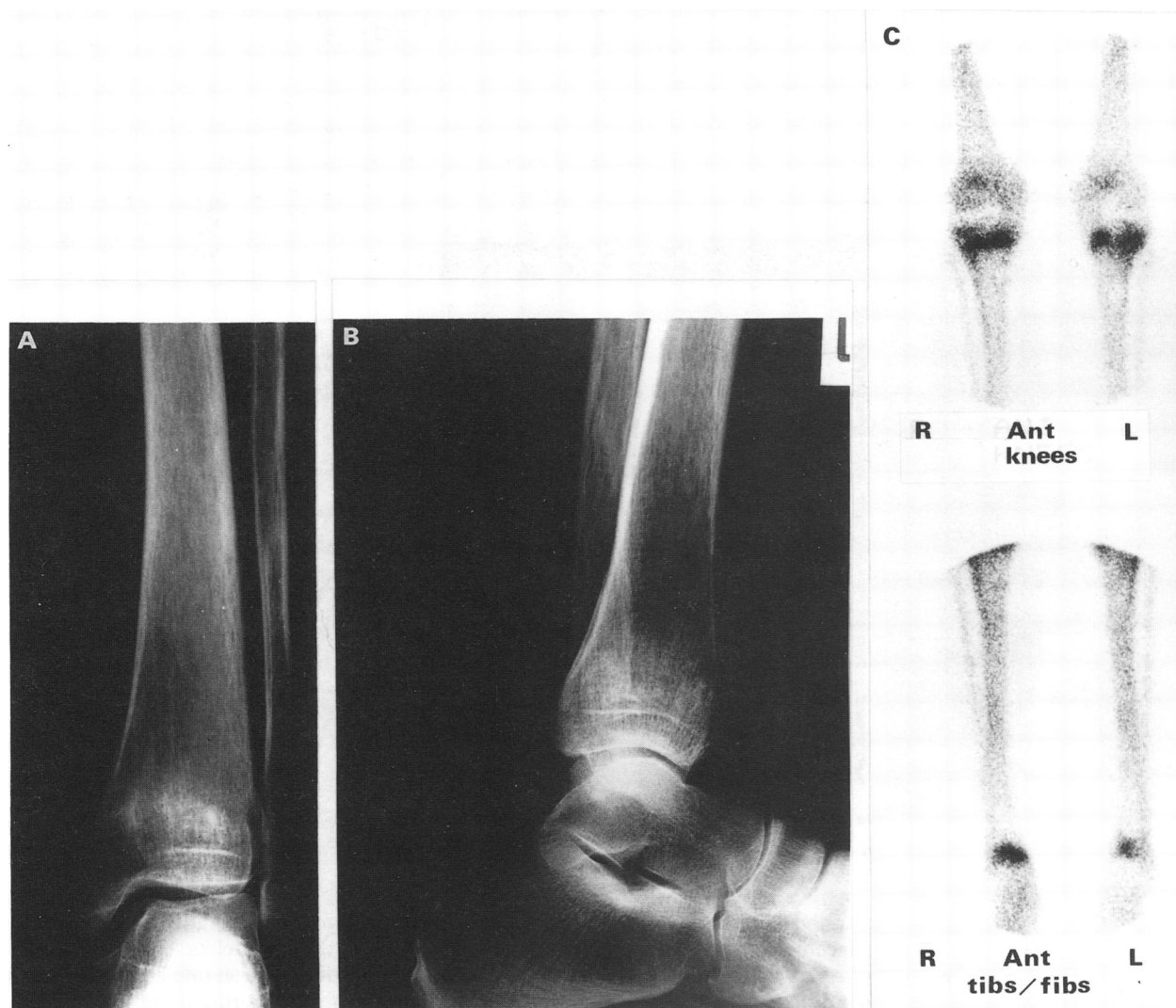


Figure 1 (A, B) Radiographs of the left ankle showing a poorly defined area of sclerosis in the distal tibial metaphysis. (C) Bone scan showing bilateral increased uptake in the metaphysal regions of the proximal and distal tibiae.

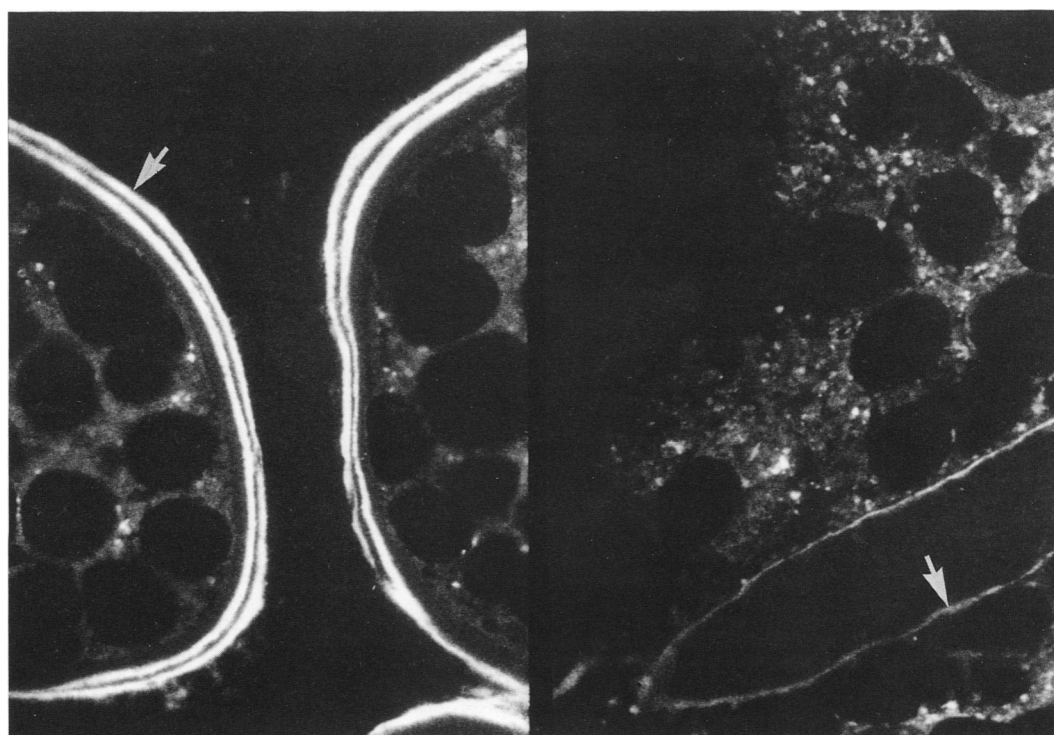


Figure 2 Bone biopsy sample showing normal osteoid thickness (left) and reduced osteoid thickness (right) (arrowed).

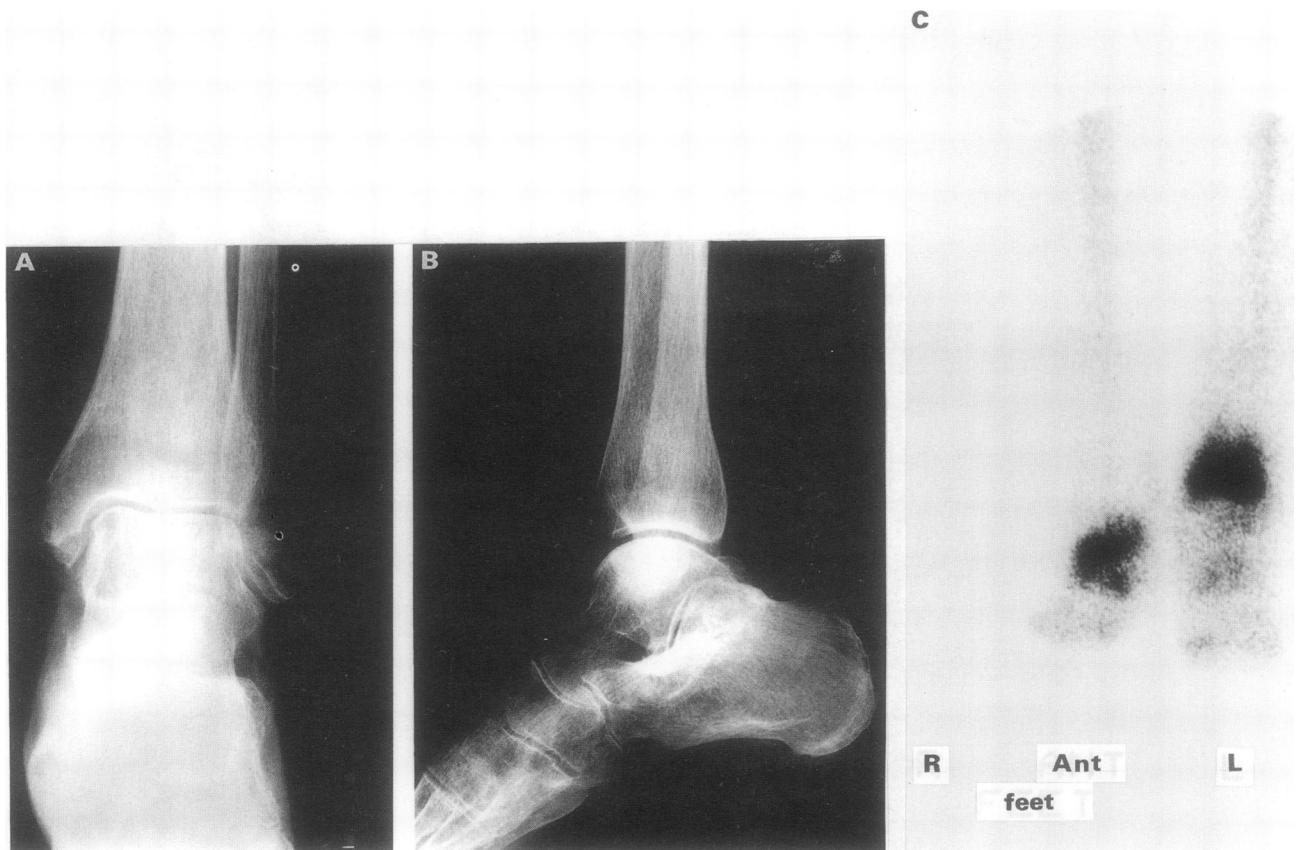


Figure 3 (A, B) Anteroposterior and lateral radiographs of the left ankle showing osteopenia but no evidence of fracture. (C) Bone scan showing increased uptake consistent with a fracture in the distal left tibia.

post-menopausal and had never received hormone replacement therapy.

Radiographs of the left ankle showed osteoporosis but no evidence of stress fractures (figs 3A and B). Radiographs taken two months later did not show callus formation. Radiographs of her hands and feet showed erosive changes of rheumatoid arthritis. A bone scan showed increased blood pool activity and delayed technetium uptake in the distal left tibia, suggestive of stress fracture (fig 3C). Increased technetium uptake was also seen in her knees, wrists, the small joints of her hands and feet, and in the right ankle joint, in a pattern consistent with rheumatoid arthritis.

Haemoglobin was 127 g/l, white blood cell count $8.7 \times 10^9/l$, platelets $284 \times 10^9/l$, and erythrocyte sedimentation rate 25 mm/h. Serum biochemistry was normal. Serum alkaline phosphatase was 160 U/l (normal range 20–95 U/l), but other liver function tests were normal. Serum calcium was 2.38 mmol/l, phosphate 0.98 mmol/l, osteocalcin 3.1 mg/ml (normal range 2.1–8.1 mg/ml), 25-hydroxyvitamin D 37 nmol/l (normal range 18–128 nmol/l), 1,25-dihydroxyvitamin D 74 pmol/l (normal range 46–207 pmol/l), and parathyroid hormone 0.16 ng/ml (normal <0.4 ng/ml).

Forearm bone mineral density was significantly reduced, whereas the lumbar spine bone mineral density was pseudoelevated owing to the presence of radiologically documented facet joint osteoarthritis (table). Iliac crest bone histomorphometry showed reduced osteoid surfaces and osteoid thickness, and a low bone formation rate (table). There were no features of osteomalacia or hyperparathyroidism.

Methotrexate was stopped with the resolution of symptoms after two months. Within weeks the patient had a flare of her rheumatoid arthritis which did not respond to sulphasalazine or prednisone by mouth. The patient asked to begin taking methotrexate again as this was the only drug which had any effect on her arthritis. A dose of methotrexate 15 mg/week was required to control her rheumatoid arthritis. After three months of treatment pain, swelling, and bone tenderness recurred in her legs, once again requiring methotrexate to be stopped before the symptoms resolved.

Bone mineral estimations and iliac crest histomorphometry in patients with methotrexate osteopathy

	Patient 1	Patient 2	Normal range
Osteodensitometry			
Distal radius (units)*	38.5	9.6	16–42.8
Lumbar spine (g/cm ²)†	0.91	1.3	0.9–1.4
Histomorphometry‡			
Cancellous bone area (%)	19.4	16.8	18.6–25.4
Osteoid area (%)	1.1	0.5	1.2–3.0
Total osteoid surface (%)	6.5	4.2	9–13.9
Osteoid thickness (μm)	7.8	6.5	9.4–12.0
Osteoblast surface (%)	3.2	1.8	5.6–10.8
Osteoclast surface (%)	0.4	1.2	0.6–2.2
Mineral appositional rate (μm/day)	0.0	0.48	0.60–0.80
Mineralising surface (%)	15§	5.6	6.0–11.2
Bone formation rate (μm ³ /μm ² /day)	0.0	0.02	0.04–0.09
Aluminium stain	Negative	Negative	
Iron stain	Negative	Negative	

*Forearm osteodensitometry was measured by single photon absorptiometry using a Noro osteodensitometer.

†Spinal osteodensitometry was measured by dual photon absorptiometry using a Norland 2600 dichromatic base osteodensitometer.

‡Method of Diamond *et al.*¹¹

§Only single tetracycline labels.

Discussion

Methotrexate osteopathy is a recognised disorder with characteristic clinical and radiographic features.⁷ Our two patients who presented with bone pain, swelling, and metaphyseal fractures are, to our knowledge, the first reported patients with rheumatic disease with methotrexate osteopathy.

Methotrexate has a reversible effect on bone when used in the treatment of malignancy in childhood.³⁻⁷ In children long term methotrexate treatment by mouth for acute lymphocytic leukaemia has been shown to cause bone pain and fractures, usually in the legs but occasionally in the arms and spine.³⁻⁷ Radiographs have shown osteoporosis, fractures, and multiple transverse bands in the metaphysis. The bone pain usually improves three to four weeks after discontinuing the methotrexate, though the radiographic changes take about four months to resolve.³ Delayed healing of fractures has also been reported, with bone union not occurring until the methotrexate has been discontinued.⁶ Abnormalities in the bone scans may precede radiographic changes.

In our patients the symptoms of bone pain, tenderness, and swelling occurred after long term treatment with low doses of methotrexate. The pain was sufficiently severe to interfere with walking and resolved over two to three months, slower than that previously described in children,³ presumably owing to the decreased regenerative capacity of aging bone. Fractures were evident on bone scans before any radiographic changes were seen.

A dose dependent effect of methotrexate on bone mineral density has been shown in adults treated for osteosarcoma and has been attributed to the inhibition of osteogenesis.⁸ It was concluded that high doses of methotrexate may result in a higher incidence of spontaneous fractures in elderly subjects in whom senile osteoporosis is also present.⁸

In our patients bone mineral density measurements were reduced and bone histomorphometry showed a low bone turnover state with reduced osteoid matrix formation. The reduction in osteoblast surfaces, osteoid matrix parameters, and tetracycline labelling is similar to the findings in animals where a reduction in bone formation rates, osteoid volume, and osteoid thickness is apparent.⁹ Our patients were all active, did not consume alcohol, and did not have a history of long term treatment with corticosteroids by mouth. Moreover, iron and aluminium stains were also negative in the bone biopsy specimens, thereby

excluding other potential factors which could have inhibited osteoblast function.

There are two theories about the toxic effects of methotrexate on bone. Increased osteoclastic bone resorption based on the finding of increased urinary and faecal calcium excretion has been proposed in patients taking methotrexate, but there have been no studies showing histomorphometric evidence of bone resorption.⁹ On the other hand, short term administration of methotrexate in the rat produced a 60% reduction in bone formation rates, with a toxic effect on osteoblasts being reflected by reduced osteoid volume and thickness,¹⁰ findings similar to those seen in our patients. This suggests that methotrexate, an inhibitor of protein synthesis, may be toxic to osteoblasts by inhibiting the recruitment of osteoblasts from the progenitor osteoblast stage and function. Furthermore, the reduced bone turnover state may also be detrimental and predispose to delayed microfracture repair.

In conclusion, we have described two adult patients who had features consistent with methotrexate osteopathy. Bone biopsy samples were consistent with osteoblast inhibition as a consequence of methotrexate action on the bone cells. When given in low doses for prolonged periods, methotrexate may be an additional risk factor for osteoporosis, especially in post-menopausal women, who already have multiple risk factors for this disorder.

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